REMARKS

Claims 1, 3, 18 and 21 presently appear in this case. No claims have been allowed. The present amendment is intended to supplement applicant's amendments of September 18, 2009, and October 7, 2009. Reconsideration and allowance are respectfully urged.

Claims 15-17 have been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cell necrosis or a neurodegenerative disorder associated therewith, does not reasonably provide enablement for prevention of cell necrosis or a neurodegenerative disorder associated therewith. The examiner states that the term "prevent" means to stop from occurring and thus requires a higher standard for enablement than does "therapeutic" or "treat." Applicant disagrees with the examiner; however, in order to facilitate the examination procedure, claims 15 to 17 have been cancelled.

In the examiner's response to argument against the 112 rejection (page 11 of the Office Action), the examiner cites the phrase "'both inhibitors were not able to protect the cells from KCN induced cell death by themselves" present in the affidavit filed on December 29, 2008 (see page 2, 3rd paragraph, lines 4-5). The Examiner is of the opinion that the cited expression is evidence that claim 15, which is only drawn to the use of elastase inhibitor, is not sufficient to protect the cells from KCN induced cell death. This part of the argument is respectively traversed. The language quoted by the examiner was unfortunate as it left an impression that is inaccurate and not supported by the very Figure which was being explained. The sentence which the examiner quotes read, "Both inhibitors were not able to protect the cells from KCN induced cell death by themselves." It should more accurately and

less ambiguously read, "Each inhibitor by itself was able to partially protect the cells from KCN induced cell death." This language is fully supported by the data and the figures. The way the examiner interpreted this paragraph is not. If necessary, the declarant will file a supplemental declaration clarifying this point. In any event, it is untrue that elastase inhibitor by itself provides no protection. This is simply unsupported by any of the data in the specification and the declaration.

Also, in Examples 5 and 9-11, pages 16-18, the specification could be incorrectly interpreted as meaning that the elastase inhibitor was inactive by itself (contrary to the results that have been shown). To eliminate this ambiguity, the specification has now been amended to correct these passages to state that the elastase inhibitor, in the absence of KCN, had no effect on cell viability. This is not new matter as the results clearly show cell protection against KCN toxicity.

Claims 1, 4, 15 and 17 have been rejected under 35 U.S.C. 102(b) as being anticipated by Gyorkos. The examiner states that Gyorkos teaches administering an elastase inhibitor to a host in need thereof, such as those in need of treatment for Alzheimer's disease (AD). The examiner notes that Gyorkos specifically teaches inhibiting human neutrophil elastase that is secreted by cells. The examiner considers that if the elastase is secreted by cells, it must also be present inside the cells in order to be secreted, thus meeting the claim limitations. The examiner assumes that the inhibitors of Gyorkos are inherently capable of entering cells. This rejection is respectfully traversed.

On page 6 and 7 in the response of September 18, 2009, strong arguments are presented against the assumption that the inhibitors of Gyorkos are inherently capable of entering cells. In the 2nd paragraph of page 6 it is said that "not all enzyme inhibitors are

capable of passing through a cell membrane." One might add that the specification, in Example 7, pages 16-17, gives an example of such an impermeable inhibitor (elastinal).

On page 7 in the response of September 18, 2009, we cite Heneka and O'Banion to show that neutrophils are not associated with Alzheimer's disease. The present inventor has reviewed the Alzheimer literature for additional support for this notion. She reported that she has not found "even one reference on AD and neutrophil elastase in brain."

Also on page 7, second paragraph, it is stated that "while various poly-morphonuclear leukocytes (PMNs) may be involved in Alzheimer's disease, neutrophils are not among them." This phrase is somewhat misleading and we would like to rephrase this sentence to read "The art fails to show a link between recruitment of PMNs, including neutrophils, in the brain and senile plaques." Please read applicant's remarks of September 18, 2009, in light of this correction.

Claims 15 and 17 have been rejected as being anticipated by Miyano. The examiner states that Miyano teaches a method of administering an elastase inhibitor for the management or alleviation of elastase mediated diseases, such as, arthritis. As to the recitation that the elastase inhibitor be capable of entering cells, the examiner states that Miyano teaches a variety of compositions for various administrations of the inhibitor at column 10, and that there is reasonable basis, absent evidence to the contrary, that the inhibitors of Miyano are capable of entering cells. The examiner states that this rejection is applicable to claims 15 and 17 as they are directed to prevention, which is readable on the administration to any patient population.

Claims 15 and 17 have been cancelled so this rejection in now moot.

Claims 1, 4, 15 and 17 have been rejected under 35 U.S.C. 102(b) as being anticipated by Miyano as evidenced by Proskuryakov. The examiner states that Miyano

teach administering an elastase inhibitor to a host in need thereof for the management or alleviation of elastase mediated diseases, such as arthritis, and specifically rheumatoid arthritis. The examiner states that Proskuryakov teach that inflammatory diseases are associated with cell necrosis and since Miyano teach inflammatory diseases such as rheumatoid arthritis, the patient population of claim 1 is met since the diseases are associated with cell necrosis. The examiner states that Proskuryakov is cited as a universal fact to show that the patient population of Miyano meets the limitation of the instant claims. This rejection is respectfully traversed.

Amended claim 1 reads on a method for inhibiting necrosis in neuronal, Purkinje, hippocampal, pyramidal or glial cells, or treating a neurodegenerative disorder associated with necrosis of said cells, comprising administering an elastase inhibiting agent in an amount sufficient to inhibit necrosis of said cells, wherein said elastase inhibiting agent is capable of entering said cells.

In addition to the arguments already presented, please note that claim 1 has been amended and refers now to a method for inhibiting necrosis in neuronal, Purkinje, hippocampal, pyramidal or glial cells or treating a neurodegenerative disorder associated with necrosis of said cells. Miyano mentions that the subject derivatives are useful to prevent or alleviate malconditions related to or arising from human leukocyte elastase imbalance and harmful degradation of elastin and other proteins, and that such diseases would include emphysema, atherosclerosis, connective tissue disease, rheumatoid arthritis, rheumatoid joint disease, pseudoxanthoma elasticum, X-linked cutis laxa, Menke's kinky-hair syndrome and Ehlers-Danlos syndrome, Type V as well as other diseases resulting from the harmful effect of elastase. Thus, Miyano does not envision and therefore does not anticipate inhibiting

necrosis in nerve or glial cells or treating a neurodegenerative disorder associated with necrosis of said cells.

In the response to the two obviousness rejections, one could add that neutrophils that are activated by the inflammatory process clearly die by apoptosis – not by necrosis (see enclosed Witko-Sarsat et al., 2000, p. 633 paragraph I.D.2, which will be submitted in an IDS next week). Thus, Gyorkos would not have motivated an average person skilled in the art and thus familiar with this fact to inhibit necrosis by administering an elastase inhibiting agent in an amount sufficient to inhibit necrosis of said cells, wherein said elastase inhibiting agent is capable of entering said cells.

Another fact that should be mentioned is that necrosis may elicit inflammation but there is a time lapse between the necrotic process and the inflammatory processes. One good example is Myocardial Infarction; Necrosis occurs 4-12h after the MI while neutrophils begin to infiltrate between 12-24 h after the stroke (see Robbins and Cortan. Pathologic Basis of Disease, 7th Edition. Elsvier Saunders Chapter 12 p.579. The Heart by Frederick J. Schoen, which will be submitted as part of an IDS next week). It follows that neutrophils that are involved in an inflammatory process cannot be the target for inhibition of necrosis since the neutrophils are not present at the site of necrosis at the time when it can still be treated, i.e., before the cells rupture and die. Thus, Gyorkos would not have motivated an average person skilled in the art and thus familiar with the temporal relation between necrosis and inflammation to inhibit necrosis by administering an elastase inhibiting agent in an amount sufficient to inhibit necrosis of said cells, wherein said elastase inhibiting agent is capable of entering said cells.

It is requested that the present amendment be considered in conjunction with applicant's amendments of September 18 and October 7, 2009, and that all of the rejections

of record be reconsidered and withdrawn in view of the cumulative arguments presented in these papers. As all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112, reconsideration and allowance are earnestly solicited.

Respectfully submitted,

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